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Safety Assessment of One Day Treatment of Liquorice Extract in Female Sprague Dawley Rats

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Abstract: This study aimed to provide preliminary data on the safe use of liquorice extracts for herbal product consumers. Female Sprague Dawley rats received a single-day treatment with liquorice extract (50–2000 mg/kg) or distilled water (control). Liver and kidney functions were evaluated through blood biochemical analysis, gross, and histological evaluation. This animal study adhered to the OECD Test Guideline 423. Fifteen female SD rats, aged 16 weeks, were randomly assigned to five groups (n = 3). The control group received distilled water, while treatment groups T1, T2, T3, and T4 were administered liquorice extract at doses of 2000, 200, 100, and 50 mg/kg via oral gavage. Body and organ weights (liver, kidney, heart) were measured. Blood samples were collected to assess serum biochemical markers, including alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), creatinine, and urea levels. Data were analysed using Dunnett's tests, with $p < 0.05$ denoting statistical significance. No significant changes in body or organ weights occurred across groups. Liquorice extract had no effect on ALT or GGT. Serum creatinine decreased ($p < 0.05$) at 200 mg/kg, and serum urea decreased at 50 mg/kg compared with controls. A single-day liquorice extract treatment (50–2000 mg/kg) was safe and caused no hepatic or renal toxicity in female SD rats.

Keywords: Liquorice extract, hepatic function, renal function, serum biochemical marker

1. Introduction

Herbal treatments are increasingly recognized as potential alternatives for treating various diseases worldwide. One such herb is liquorice, scientifically known as Glycyrrhiza glabra (Sharifi-Rad et al., 2021). It was the most prescribed herb in Ancient Egyptian, Roman, Greek, East China, and the West from the Former Han era. Various species of liquorice are cultivated in Europe, the USA, southwestern Asia, and Central Africa, the Middle East, Afghanistan, and the northern part of India. In addition, England, Spain, Iraq, Turkey, China, and Sicily commercially cultivate liquorice. Other countries that also produce liquorice include Pakistan, Azerbaijan, Turkmenistan, and Uzbekistan (Wahab et al., 2021).

Liquorice extract has received significant attention in research due to its potential benefits, including anti-inflammatory, immunostimulatory, and antimicrobial properties and hepatoprotective effects. Adverse effects have mainly been associated with high doses, primarily due to glycyrrhizin, which leads to cortisol accumulation and can cause pseudohyperaldosteronism, resulting in health issues such as elevated sodium levels, decreased potassium levels, and water retention (Murray, 2020).

Although the literature on the gross and histological effects of liquorice extract on vital organs in rats remains limited, existing studies suggest promising biological activity, particularly in promoting wound repair. For instance, Assar et al. (2021) reported that administration of liquorice alcoholic extract significantly increased total and differential leukocyte counts, enhanced neutrophil phagocytic function, and upregulated antioxidant biomarkers such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and reduced glutathione (GSH), while decreasing malondialdehyde (MDA), a marker of oxidative stress. Histopathological examination revealed complete re-epithelialization and increased collagen formation. Immunohistochemical analysis showed elevated expression of α-smooth muscle actin (α-SMA), platelet-derived growth factor receptor alpha (PDGFR-α), fibroblast growth factor receptor-1 (FGFR1), and cytokeratin 14 in treated groups—findings that

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support the extract's role in enhancing angiogenesis and tissue regeneration (Assar et al., 2021). In contrast to previous studies that focused primarily on wound healing and inflammatory responses (Assar et al., 2021), our investigation provides additional insight into the systemic safety profile of liquorice extract, specifically its effects on liver and kidney function. The absence of significant changes in ALT, GGT, and organ weights suggests short-term tolerance. Furthermore, observed reductions in serum creatinine and urea levels may indicate a potential renoprotective effect. However, variations in experimental design, such as dosage, exposure duration, and animal species, highlight the need for further research to establish comprehensive safety and dosing protocols.

Liquorice extract, including herbal teas, capsules, tablets, and liquid extracts, is commonly consumed orally. It is known for its potential soothing and sweet flavour and is used for digestive health and respiratory relief. Topically, it is applied in creams, ointments, and gels for skin conditions such as eczema and psoriasis. For respiratory issues, it is available as lozenges, syrups, or inhalation products (Wang et al., 2022).

The phytochemical analysis of liquorice extract from Glycyrrhiza species reveals a rich mixture of bioactive compounds, particularly in the roots. It contains sugars, starch, bitters, resins, essential oils, tannins, and nitrogenous compounds. The key constituents of Glycyrrhiza glabra are triterpenoid saponins, flavonoids, coumarins, alkaloids, amino acids, volatile components, and polysaccharides, with over 60 compounds identified (Dang et al., 2024). More than 300 flavonoids, such as liquiritin and isoliquiritin, give liquorice its yellow colour, while bioactive flavonoids like licochalcone C and glycosides enhance its therapeutic potential. Triterpenoid saponins like glycyrrhizin are notable for their role in healing gastric ulcers, while coumarins such as liqcoumarin exhibit antiviral properties. Liquorice's essential oils also contain α-pinene and β-caryophyllene (Husain et al., 2021). In summary, liquorice extract is a complex mixture of bioactive compounds with diverse pharmacological activities, supporting its use in various medicinal applications when properly dosed.

The COVID-19 pandemic has sparked considerable interest in liquorice, particularly its active component, glycyrrhizic acid, which has shown potential in combating COVID-19 due to its antiviral and anti-inflammatory properties. Research is ongoing to assess its health benefits. The pressing need for effective and well-tolerated treatments has led to growing interest in traditional herbal remedies as potential adjuncts for viral diseases, including COVID-19 (Gomaa & Abdel-Wadood, 2021). Due to these pre-existing and recent developments and the need for updated, significant evidence, further research is necessary to determine its safety and effectiveness in humans.

Since most recent studies focus primarily on the pharmacological characteristics and chemical composition of liquorice extract, the current research gap in the literature becomes evident. As a result, there is a scarcity of research examining its impact on the biochemistry and histology of rats. These findings emphasise the importance of preclinical animal studies to understand the underlying mechanisms, even though human case reports have highlighted instances of adverse effects, such as hypertension, hypokalaemia, and metabolic disturbances, as mentioned in the cited study (Sharifi-Rad et al., 2021). Exploring the histological outcomes in different organs is vital for gaining insights about the safety and efficacy of liquorice as a therapeutic agent (Sharifi-Rad et al., 2021). This study aims to address this gap by investigating the less-explored adverse aspects of liquorice extract, providing a more comprehensive understanding of its impact on human health and assisting in assessing the potential risks and benefits of its consumption.

The main aim of this study is to investigate and determine the safe administration of liquorice extract treatments. To achieve this aim, we have set objectives to guide us towards the aim. Our primary objective is to observe and compare the biochemical and histological changes of vital organs in female Sprague Dawley (SD) rats given liquorice extract treatments after 1 day, as compared with the distilled control group treated with water. In this way, we can determine if there are significant differences between the groups, which allows us to conclude. Our secondary objective is to study the effects of various doses of liquorice extract treatment (2000 mg/kg, 200 mg/kg, 100 mg/kg, and 50 mg/kg concentrations) on the vital organs of rats after 1 day. The results obtained from this study will be significant to the community regarding the use of liquorice extract treatments on individuals.

In conclusion, although prior research has yielded numerous benefits and some drawbacks, further investigation is necessary to provide a comprehensive understanding of the possible pathological impacts on vital organs at the histological and biochemical levels. With liquorice's rich history and diverse health benefits, this study seeks to contribute to the growing interest in traditional herbal remedies and their role in promoting overall well-being and addressing pressing health challenges.

2. Materials and methods

2.1 Raw Materials and Extractions

Liquorice roots were purchased from a local traditional Chinese medicine supplier in Klang Valley. The dried and pulverized liquorice roots were weighed and macerated using distilled water from an ultrapure system in a conical flask with percolation in boiling water for 30 minutes in a hot water bath maintained at 100°C. The mixture was allowed to cool to room temperature and filtered after 24 hours using sterile filter paper. The extract was freeze-dried to obtain a constant weight of fine powder and stored in an airtight container for further use.

2.2 Selection of Animals

A total of 15 healthy female Sprague Dawley (SD) rats with 150 g ± 20 g body weight were used for this study. All groups of rats were fed a standard rodent pellet diet and maintained in the animal holding room under a 12-hour light/dark cycle at 25 ± 2ºC. The animal work was conducted according to the procedure approved by the Animal Ethics Committee of UTAR (U/SERC/253/2022).

2.3 Study Design

A total of 15 randomly selected female Sprague Dawley rats were divided into five groups, each consisting of three rats (n=3).

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Table 1. Body weights

Body Weight (g)	Control (distilled water) [n=3]	T1 (2000 mg/kg) [n=3]	T2 (200 mg/kg) [n=3]	T3 (100 mg/kg) [n=3]	T4 (50mg/kg) [n=3]
Body weight (g)	220.5 ± 14.7	222.4 ± 15.2 (ns)	221.7 ± 21.6 (ns)	221.0 ± 13.6 (ns)	220.6 ± 7.7 (ns)

Data were expressed as mean ± SD; Analysed with Dunnett's test
ns: non significant difference compared with the control

The groups included one control group, which received distilled water orally, and four experimental groups (T1, T2, T3, and T4). The experimental groups received one day of liquorice extract at doses of 2000 mg/kg, 200 mg/kg, 100 mg/kg, and 50 mg/kg, respectively. Animal care and handling followed OECD 423 guidelines.

2.4 Blood Sampling and Biochemical Analyses

After 24 hours of the last treatment, blood samples were collected via cardiac puncture under anaesthesia using carbon dioxide to evaluate liver and kidney function. Liver function tests measured ALT (U/L) and GGT (U/L), while kidney function tests assessed creatinine (mmol/L) and urea (mmol/L) within a diagnostic laboratory. Relative organ weights were calculated using the formula: average organ weight divided by average body weight.

2.5 Histopathological Study

The vital organs of the rats from both the control and the liquorice treatment groups were removed after the rats were sacrificed. The stomach was opened along its greater curvature, flattened, and pinned onto a corkboard with the mucosal surface facing upwards. Great care was taken to avoid damaging the mucosal surface. Tissue samples from each group were obtained and fixed in 10% formaldehyde for 24 hours. The fixed specimens were dehydrated, cleared, and embedded in paraffin. Each section was 5 microns thick, and sections were obtained using a rotary microtome (brand: RWD Life Science). Using a water bath at 37℃, individual wax sections were flattened onto glass slides and allowed to dry overnight in an incubator. The sections were dewaxed with xylene, rehydrated through descending grades of alcohol, and washed in distilled water. Subsequently, the sections were stained using routine Harris's haematoxylin and eosin technique, mounted with Dibutylphthalate Polystyrene Xylene (DPX), and examined by light microscopy. Histological changes in the organs were compared between the control and treatment groups.

2.6 Statistical Analysis

The results for body weight, relative organ weights, and blood biochemical tests were presented as mean ± standard deviation. Dunnett's test was applied to determine significant differences between experimental and control groups. A p-value of <0.05 was considered statistically significant.

3. Results

Compared with the control group, there were no significant changes in body weight (Table 1) and relative organ weight for liver, kidney, and heart in all liquorice treatment groups (Table 2). Female rats treated with a single dose of liquorice extract did not show significant changes in serum levels of ALT and GGT compared to the control group (Table 3). A significant ($p<0.05$) decrease in serum levels of creatinine and urea was observed in rats treated with 200 mg/kg and 50 mg/kg of liquorice extract, respectively, compared to the control group (Table 3).

There are no observable changes in heart tissue on the histopathological slide. The lack of necrosis, fibrosis, or inflammation indicates that liquorice extract did not cause cardiotoxicity at this dose. Kidneys showed occasional thinning of Bowman's space in a few glomeruli and haemorrhages. The liver showed minimal cytoplasmic vacuolation of hepatocytes surrounding the central vein. Mild lymphocytic infiltration was observed in the portal triad with intact architecture and absence of fibrosis. Hence, these histopathological findings are consistent with the biological outcomes of our investigation.

4. Discussion

Changes in body weight and organ weight are both important indicators of drug toxicity; however, changes in organ weight show higher sensitivity in this regard, especially if alterations in body weight are inevitable (Lazic et al., 2020). Based on the results obtained, single-day usage of liquorice did not significantly affect the body weights or the relative organ weights of the heart, kidneys, and liver. These findings imply a lack of toxicity after one day; however, biochemical and histological assessments of the aforementioned organs were conducted to enhance the sensitivity of this evaluation. The serum samples of the rats were tested for levels of Alanine Transaminase (ALT), Gamma-glutamyl Transferase (GGT), creatinine, and urea. ALT levels in the serum increase when structural damage to the liver occurs, causing this enzyme to leak out of damaged cells into the bloodstream (Thakur et al., 2024; Moriles & Azer, 2020). Serum GGT, alternatively, may be used to indicate bile duct cell necrosis or bile duct hyperplasia (GGT – EClinpath, n.d.; Sun et al., 2021). In our study, rats treated with liquorice extract showed no significant differences in ALT or GGT levels compared to the control group, suggesting no hepatotoxic effects following a single day of treatment. The observed decrease in creatinine and urea levels may indicate enhanced kidney function, possibly due to improved blood flow or changes in the filtration process, although our histological research revealed renal haemorrhage in

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Table 2. Relative organ weights

Organ Index (g/100 g *b.w.*)	Liquorice Extract (mg/kg *b.w.*)				
	Control (distilled water) [n=3]	T1 (2000 mg/kg) [n=3]	T2 (200 mg/kg) [n=3]	T3 (100 mg/kg) [n=3]	T4 (50mg/kg) [n=3]
Liver	2.73 ± 0.03	2.78 ± 0.02 (ns)	2.78 ± 0.02 (ns)	2.74 ± 0.02 (ns)	2.75 ± 0.02 (ns)
Kidney	0.50 ± 0	0.52 ± 0 (ns)	0.56 ± 0 (ns)	0.56 ± 0.01 (ns)	0.53 ± 0.01 (ns)
Heart	0.31 ± 0.02	0.31 ± 0 (ns)	0.31 ± 0 (ns)	0.32 ±0.01 (ns)	0.33 ± 0.01 (ns)

Data were expressed as mean ± SD; Analysed with Dunnett's test
ns: non significant difference compared with the control

Table 3. Effect of 1 day of Oral Administration of Liquorice Extract on Serum Biochemical Parameters

Parameters	Control (distilled water) [n=3]	T1 (2000 mg/kg) [n=3]	T2 (200 mg/kg) [n=3]	T3 (100 mg/kg) [n=3]	T4 (50mg/kg) [n=3]
Liver Function					
ALT (U/L)	115.5 ± 79.90	68 ± 4.24 (ns)	1.39 ± 2.83 (ns)	67.5 ± 3.54 (ns)	41.5 ± 3.54 (ns)
GGT (U/L)	4.5 ± 0	4 ± 0 (ns)	5 ± 0 (ns)	4 ± 0 (ns)	4 ± 0 (ns)
Renal Function					
Creatinine (mmol/L)	23.35 ± 2.3	22.9 ± 0.57 (ns)	13.25 ± 0.07* *(p < 0.05)*	26.05 ± 1.48 (ns)	26.6 ± 1.27 (ns)
Urea (mmol/L)	7.5 ± 0.7	7.1 ± 0.07 (ns)	6.75 ± 0.35 (ns)	7.2 ± 0 (ns)	5.8 ± 0.14* *(p< 0.05)*

Data = mean ± standard deviation; Analysed with Dunnett's test
ns: non significant difference compared with the control; *p<0.05: significant difference compared with the control

response to a 200 mg/kg dosage. This action may be explained by the capacity of glycyrrhizin, a major component in liquorice, to mimic certain hormones and influence renal function. Even though this reduction could appear beneficial, additional research is necessary to exclude any underlying damage or negative effects. Serum creatinine and urea are important indicators for renal function concerning their glomerular filtration and are usually elevated in renal impairment (Brookes & Power, 2022; Gounden & Jialal, 2024). Our study showed a decrease in serum creatinine and urea in specific groups of rats. However, variations in these parameters may also be caused by non-renal factors, such as muscle mass and diet ("Biomarkers in Acute Kidney Injury," 2020); thus, these findings may be unrelated to the rats' treatment with liquorice extract, particularly as reduced serum creatinine and urea were only found in a single group of rats, respectively.

While the biochemical assessment suggests a lack of toxicity, histological examination was performed on the heart, liver, and kidneys of the rats to verify this with greater sensitivity. Upon histological analysis, the kidneys and liver after a single day of usage of liquorice showed minimal alterations. These findings were also seen in the control group, indicating that these histological changes may not be related to liquorice use but might have potentially resulted from handling conditions of the rats or environmental stressors. In another study in 2020 (Kim et al., 2020), the administration of liquorice extract in various dosages and periods produced no biochemical or histological alterations, and organ body weights remained within normal limits, which aligns with the results of our investigation.

This study evaluated the acute oral toxicity of liquorice extract after a single day. This is useful in determining the safe dose level of liquorice extract, its potential to cause acute toxicity, and possible target organ toxicity (Pawar et al., 2023). However, the duration of one day may be insufficient to detect the full extent of any acute and chronic effects of liquorice extract on the organs studied, as adverse effects related to acute toxicity typically manifest within 14 days (Pawar et al., 2023). Therefore, further studies should be conducted to observe the effects of liquorice extract on the organs of rats after longer durations, e.g., 30 days. Additionally, controlled clinical trials may prove valuable to assess the effects of liquorice extract consumption specifically in humans.

Water is a highly suitable solvent for plant extraction due to its non-toxic, safe, and environmentally friendly nature, making it ideal for food, pharmaceuticals, and cosmetics applications without leaving harmful residues (Lajoie et al., 2022). It is widely

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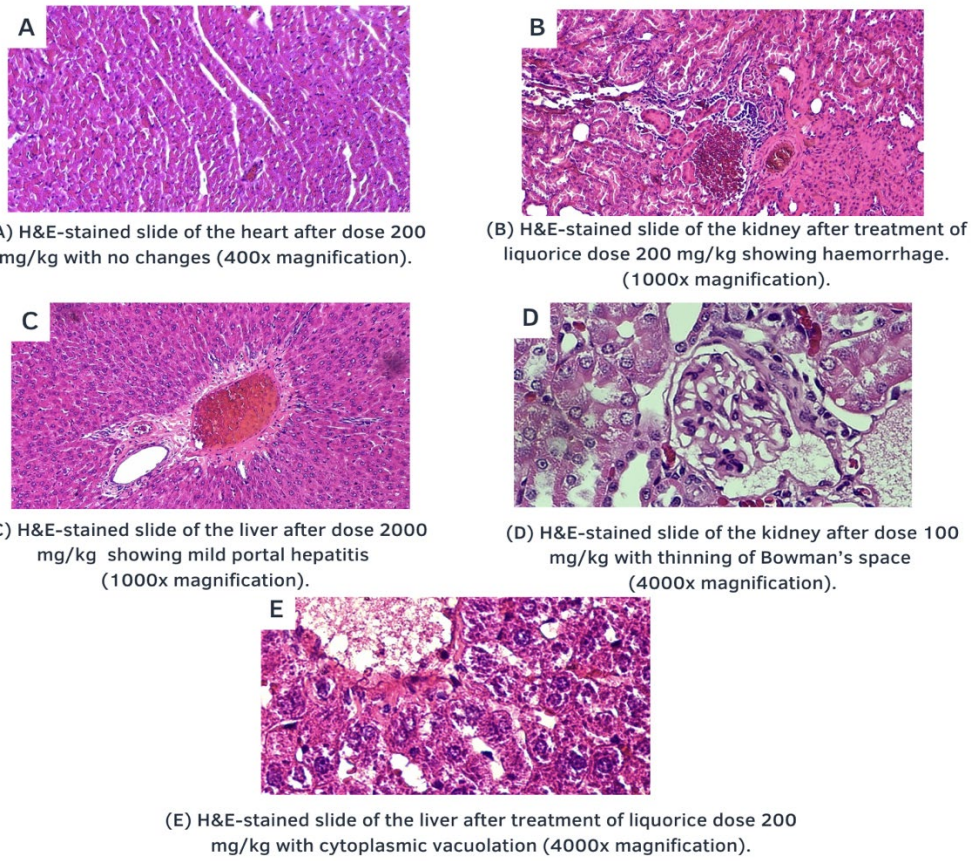

Figure 1. Histological changes in the vital organs of the rats after 1 day treatment of liquorice extract

available and cost-effective, making it practical for large-scale extractions. Water efficiently extracts polar bioactive compounds such as phenolics, flavonoid glycosides, and tannins, which are recognized for their antioxidant and health-promoting properties. The extraction efficiency can be further improved by acidification, such as acetic or hydrochloric acid (Plaskova & Mlcek, 2023). Water can also be combined with organic solvents, such as ethanol, in binary mixtures to expand the range of extracted compounds and increase overall yield. Additionally, water-based extraction is gentler, reducing the risk of thermal degradation or oxidation, making it suitable for heat-sensitive bioactive compounds (Plaskova & Mlcek, 2023). As a result, water provides a flexible, sustainable, and efficient method for plant extraction in various industries, making it an optimal solvent for the extraction of liquorice in this study.

5. Conclusion

One-day treatment with liquorice extract from 50 mg/kg to 2000 mg/kg did not produce any toxic effects on the vital organs of the rat and was safe to administer. Additionally, the unexpected reduction in creatinine and urea levels may indicate improved renal function, although further investigations are required to confirm this finding and exclude any potential adverse effects. However, it is important to acknowledge that the study's short duration and limited sample size present notable limitations. Larger, long-term studies are necessary to establish the comprehensive safety profile of liquorice extract and assess its potential therapeutic or toxic effects.

6. Acknowledgement

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